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Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease

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Abstract

***Objective*—To compare effectiveness of levodopa and levodopa combined with selegiline in treating early, mild Parkinson's disease.**

***Design*—Open, long term, prospective randomised trial.**

***Setting*—93 hospitals throughout United Kingdom.**

***Subjects*—520 patients with early Parkinson's disease who were not receiving dopaminergic treatment.**

***Interventions*—Treatment with levodopa and dopa decarboxylase inhibitor (arm 1) or levodopa and decarboxylase inhibitor in combination with selegiline (arm 2).**

***Main outcome measures*—Assessments of serial disability, frequency and severity of adverse events, and deaths from all causes.**

***Results*—After average of 5·6 years' follow up, mortality ratio in arm 2 compared with arm 1 was 1·57 (95% confidence interval 1·09 to 2·30), and difference in survival between the two arms was significant (log rank test, P=0·015). Hazard ratio adjusted for age and sex was 1·49 (1·02 to 2·16), and after adjustment for other baseline factors it increased to 1·57 (1·07 to 2·31). Patients in arm 1 had slightly worse disability scores than those in arm 2, but differences were not significant. Functionally disabling peak dose dyskinesias and on/off fluctuations were more frequent in arm 2 than arm 1. During the trial the dose of levodopa required to produce optimum motor control steadily increased in arm 1 (median daily dose 375 mg at 1 year and 625 mg at 4 years), but median dose in arm 2 did not change (375 mg).**

***Conclusions*—Levodopa in combination with selegiline seemed to confer no clinical benefit over levodopa alone in treating early, mild Parkinson's disease. Moreover, mortality was significantly higher with combination treatment, casting doubts on its chronic use in Parkinson's disease.**

Introduction

Levodopa in combination with a peripheral dopa decarboxylase inhibitor substantially improves the functional disability and quality of life of patients with Parkinson's disease, and 25 years after its routine introduction into clinical practice it remains the most effective palliative treatment. However, it fails to halt the underlying progression of disease, and the long term therapeutic response is compromised by the emergence of abnormal hyperkinetic involuntary movements, fluctuations in motor performance and mood, and psychiatric side effects.[1] Although there is no definitive clinicopathological evidence to suggest that exogenous levodopa might be harmful to surviving nigral neurones in Parkinson's disease, it has been shown to increase oxidative stress in tissue cultures, thus consolidating theoretical concerns about its potential neurotoxicity in patients.[2] It also now seems clear that levodopa does not substantially improve the life expectancy of patients with Parkinson's disease.[3]

Recently, there has been interest in the notion that the antiparkinsonian drug selegiline hydrochloride, a selective type B monoamine oxidase inhibitor, might protect failing nigral neurones in Parkinson's disease and improve life expectancy. The Parkinson Study Group in the United States reported that, in the early stages of the disease, selegiline delayed the emergence of parkinsonian disabilities and the need for symptomatic treatment with levodopa by around nine months.[4] In their initial publication they suggested that selegiline might have a beneficial effect on the natural course of Parkinson's disease through neural protective mechanisms. On longer follow up, however, they concluded that selegiline did have symptomatic effects, and a worsening of motor scores was seen two months after selegiline had been stopped.[5] It has been proposed that the putative neuroprotective effects of selegiline may not be due just to its inhibition of type B monoamine oxidase but that trophic effects and alteration of gene expression in damaged neurones may also occur.[6] However, the symptomatic antiparkinsonian effects of selegiline and the subjective end point of the DATATOP study confound the interpretation of its main findings.[7]

In 1985 the Parkinson's Disease Research Group started a study of the possible beneficial effects of combining selegiline with levodopa (with a dopa decarboxylase inhibitor) on the natural course of Parkinson's disease and the potential advantage of starting antiparkinsonian treatment with a dopamine agonist (bromocriptine).[8] The interim three year report indicated that all three treatment regimens led to improvement in baseline disabilities after one year of continuous treatment but that functional disability and physical signs had deteriorated after three years.[9] No significant differences were found between the two study arms with levodopa, but both treatments were significantly more effective than bromocriptine and produced fewer adverse reactions in the first three months of treatment. However, drug induced dyskinesias and motor fluctuations in performance

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were significantly less frequent in the group treated with bromocriptine. No significant difference in mortality was present at the time of the three year analysis. A further interim analysis in December 1994 showed that the mortality in the group treated with levodopa alone was significantly different from the rate in the group given levodopa in combination with selegiline. We therefore present disability, incidence of adverse events, and mortality for the two study arms with levodopa.

Patients and methods

PATIENTS

We recruited 782 patients between September 1985 and September 1990. Forty patients were randomly recruited somewhat earlier at University College London hospitals (1982 onwards). The patients were randomised into one of three treatment arms: levodopa and dopa decarboxylase inhibitor (arm 1), levodopa and dopa decarboxylase inhibitor combined with selegiline (arm 2), and bromocriptine monotherapy (arm 3).

Patients were eligible for inclusion in the study if they fulfilled the operational criteria for the clinical diagnosis of Parkinson's disease proposed by the Parkinson's Disease Society of the United Kingdom Brain Tissue Bank.[10] Untreated patients of any age with incapacity that in the judgment of their clinician was sufficient to merit dopaminergic treatment were eligible for inclusion. Patients who had previously received anticholinergic drugs or amantadine and those who had been considered on uncertain or incomplete evidence to be intolerant of levodopa were also considered suitable for entry. Patients who were known with certainty to have failed to respond to an adequate trial of dopaminergic drugs and those with incapacitating cognitive impairment were excluded.

STUDY DESIGN

The study received ethical approval from the Faculty of Clinical Sciences, University College London Medical School; some investigators also sought local ethical approval before starting the study. Fifty eight investigators—predominantly consultant neurologists, with some consultant physicians in geriatric medicine with a special interest in Parkinson's disease—participated in the study, which was carried out in 93 NHS hospitals.

Expected mortality figures were based on the study by Shaw *et al*, who reported mortality of 27% after six years' follow up and 57% after 12 years in a group of British men and women treated with levodopa for Parkinson's disease.[11] It was calculated that about 600 people would need to be followed for 10 years to detect a 30% difference in mortality between treatment arms (power 80%, significance 5%). This figure was chosen because in an open, uncontrolled, retrospective survey Birkmayer *et al* had shown a 30% reduction in mortality in a group of patients taking levodopa with selegiline compared with a group of patients taking levodopa alone.[12]

Treatment

Randomisation of the patients into one of three treatment regimens was carried out by an independent coordinator using random numbers tables.[13] After each patient had given informed consent, the investigators telephoned the trial office for a randomisation code, which was subsequently confirmed in writing.

Treatment in arm 1 consisted of 62·5 mg levodopa and benserazide three times daily after meals. The dose was then increased to 125 mg thrice daily and maintained for at least three months before further increases were considered. Further increments and maintenance were then left to individual investigators, but the aim of treatment was to achieve a satisfactory improvement in symptoms and functional disabilities with the lowest possible levodopa dose.

Treatment in arm 2 was started with 5 mg selegiline in the morning for a week followed by an increase to 5 mg twice daily for three weeks. At the end of this time levodopa and benserazide was added in the same way as for study arm 1, and selegiline was continued at the same dose.

Treatment in arm 3 was bromocriptine given alone. The starting dose was 2·5 mg after the evening meal. This was increased by 2·5 mg no faster than every third day to 30 mg daily taken in three divided doses with meals. Increases no faster than 10 mg weekly were then made up to a maximum dose of 40 mg thrice daily.

If peripheral dopaminergic side effects occurred in any of the study arms the investigator responsible was at liberty to prescribe domperidone, a peripheral dopamine antagonist, 20 mg thrice daily.

Outcome measures

The principal outcome measures were mortality and differences in disability scores. Patients were evaluated at baseline and then every three to four months, whenever possible by the main investigator, and preferably in the presence of one of the patient's close relatives. Disability was assessed with the Hoehn and Yahr scale,[14] the North Western University disability scale,[15] and the 12 item Webster rating scale[16] modified to include additional parameters of balance and rising from a chair. The occurrence and severity of adverse reactions—including dyskinesias, fluctuations in performance (on/off effect), and early morning dystonia—were recorded; dyskinesia, dystonia, and severity of motor fluctuation were rated on a scale of 0-3 at each visit.

Interim analyses were carried out once a year as planned from the start of the study. When significant results were found at the level used for interim testing they were reviewed by a trials committee, which decided whether to inform all investigators with a view to publication.

Patients records were flagged for mortality at the NHS Central Register. The cause of death was assigned from the death certificate by the Office of Population Censuses and Surveys in accordance with rules of the World Health Organisation.

Patients who were unable to tolerate the trial drug or gain useful functional improvement (initial improvement of 20% or more in rating scales and continuing improvement above baseline levels of disability) could either be randomised again to a different arm of the trial or withdrawn. Patients have been considered in this report only in relation to their original randomisation. Patients withdrawn from the trial were assessed annually for disability and adverse events. Analyses of disabilities, incidence of side effects, and mortality were performed once a year using a level of significance that took account of repeat testing. The analysis in December 1994 showed a significant difference in mortality between levodopa alone and levodopa and selegiline at the level used for interim testing, and the decision was taken to proceed to a full analysis of outcome measures for these two treatment groups. The difference in mortality between the bromocriptine arm and the other two study arms was not significant, and therefore no results for the bromocriptine arm of the trial are presented in this report. The study investigators were first informed of these results at a meeting in April 1995.

STATISTICAL ANALYSIS

The main analyses were conducted on a basis of intention to treat and included all 520 patients initially

randomised to arm 1 or arm 2 irrespective of whether they were subsequently withdrawn from treatment. Assessment of mortality was based on follow up to the end of 1993, whereas all other analyses were based on follow up until December 1994. The follow up was restricted for mortality because there may be a delay in receiving death notifications from the NHS Central Register.

Death rates in each arm were calculated by using total person years of follow up in each study arm as the denominator. The number of years of follow up for each patient was calculated as the time from date of entry into the trial until one of the following: date of death; December 1993 if known to be alive on that date (either seen by an investigator in 1994 or "flagged" at the NHS Central Register); date last known to be alive if lost to follow up and insufficient information to enable flagging to occur (usually the date last seen by an investigator). Eight patients in study arm 1 (levodopa) and five patients in arm 2 (levodopa and selegiline) were lost to follow up. Mortality in the two arms was compared with the χ^2 test (interim analyses), log rank test, and Kaplan-Meier survival curves.[17] Adjustments were made for age, sex, and other baseline prognostic factors with the Cox proportional hazards model, and differences in effect by subgroups were tested by including an interaction term in the model.

Investigation of average disability scores for all treatments combined showed an initial improvement in the first three months followed by a levelling off in the next 12 months, and after one year of follow up average scores displayed a roughly constant rate of decline.[9] It was therefore decided to analyse disability scores both by taking the average of all assessments in the fourth year of follow up and by taking the average of the two most recent assessments for each subject (final score). Analysis of covariance was used to assess the difference in disability scores between the treatment groups, including the baseline score as a covariate. In the analysis of "final score," months of follow up was also included in the model to adjust for any difference in length of follow up.

The incidence of side effects was calculated as rates per person year of follow up after initial randomised treatment, and significance was tested with the log rank test. Severity of dyskinesias and fluctuations in performance (on/off effects) were also compared in the two arms at four years of follow up. The difference in levodopa dose was tested with the Mann-Whitney U test.

Results

The treatment groups were similar with respect to recorded baseline characteristics of age, sex, duration of Parkinson's disease, and baseline disability scores.[9]

The median daily dose of levodopa in arm 1 and arm 2 at one year's follow up was 375 mg, and the mean doses were 420 mg and 352 mg respectively.[9] At three years the median dose of levodopa in arm 1 was 500 mg (mean 566 mg) and 375 mg (mean 423 mg) in arm 2, confirming a delayed and mild levodopa sparing effect of selegiline and giving a significant mean difference in dose of 143 mg levodopa between the two arms. At four years the difference in levodopa dose between the two arms had increased further as a result of the need for more levodopa in arm 1 (median dose 625 mg, mean 635 mg) whereas the median dose in arm 2 had remained constant at 375 mg (mean 460 mg). The mean number of daily doses in arm 1 was 4·59 (range 3-12) and in arm 2 was 4·00 (range 2-12).

A total of 49 patients (32 in arms 1 and 2) had their diagnoses revised during the course of the trial. These patients were included in the analysis to reflect clinical practice, in which it is now accepted that up to a quarter of patients will be treated for Parkinson's disease before the correct diagnosis is established. The revised diagnoses were multiple system atrophy in 18 cases, Parkinson dementia syndrome (Lewy body pathology or Alzheimer's disease) in nine, progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) in eight, essential tremor in two, masked depression in two, communicating hydrocephalus in one, frontal meningioma in one, writer's cramp in one, alcoholism in one, organic psychosis in one, cerebrovascular disease in one, and not specified in four.

Table 1 gives the main reasons for withdrawal from the trial. The number of adverse reactions was substantially greater in arm 2 than arm 1, indicating that selegiline combined with levodopa may increase the number of adverse reactions. At four years of follow up about 30% of patients in arms 1 and 2 had withdrawn from the study. Of the 37 protocol violations in arm 1 (levodopa alone), 28 were due to the introduction of selegiline after publication of the Parkinson Study Group's results.[4] Two patients from arm 1 and one patient from arm 2 were randomised again to one of the other arms.

MORTALITY

Table 2 shows the number of deaths and death rates for the two treatment groups, and figure 1 shows the Kaplan-Meier curve. The average follow up for the study of mortality was 5·6 years. The ratio of mortality in arm 2 (levodopa with selegiline) compared with arm 1 (levodopa alone) was 1·57, and the difference in survival between the two arms was significant (log rank test, P=0·0152). The hazard ratio adjusted for age and sex was 1·49 (95% confidence interval 1·02 to 2·16). After adjustment for other baseline factors (pre-treatment level of disability, duration of Parkinson's disease, and year of entry to trial) the hazard ratio increased to 1·57 (1·07 to 2·31). Thus mortality among

Table 1—*Causes of withdrawal from original randomised treatment in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline). Values are numbers of patients*

Reasons for withdrawal	Treatment arm 1 (n=249)	Treatment arm 2 (n=271)
Lost to follow up	27	26
Poor compliance	10	17
Protocol violation	37	3
Lack of response	1	0
Deterioration	31	24
Adverse reactions	7	37
Revised diagnosis	16	16
Total	129	123

Table 2—*Number of deaths and death rate (per 1000 patient years) in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline)*

	Treatment arm 1 (n=249)	Treatment arm 2 (n=271)
No of deaths	44	76
Total patient years of follow up	1372·6	1500·5
Death rate	32·1	50·7
Hazard ratio (95% confidence interval) of death rate*:		
Unadjusted	1·57 (1·09 to 2·30) (P=0·015)	
Adjusted for age and sex	1·49 (1·02 to 2·16) (P=0·036)	
Adjusted for age, sex, duration, baseline disability, year of entry to trial	1·57 (1·07 to 2·31 (P=0·018)	

*Cox regression model, treatment arm 2 *v* arm 1.

Table 3—*Causes of death in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline)*

Cause of death	Treatment arm 1		Treatment arm 2	
	No of deaths	Death rate*	No of deaths	Death rate*
Ischaemic heart disease	11	8·0	9	6·0
Cerebrovascular disease	2	1·5	11	7·3
Other cardiovascular disease	7	5·1	1	
Cancer	8	5·8	9	6·0
Parkinson's disease	7	5·1	26	17·3
Respiratory disease	5	3·6	9	6·0
Other	4	2·9	9	6·0
Cause unknown	0		2	

*Per 1000 patient years.

Table 4—*Differences in patients' mean disability scores (Webster rating) in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline)*

	No of patients in analysis		Adjusted difference in disability score (95% confidence interval)*	P value
	Treatment arm1	Treatment arm2		
Years 3 and 4 of follow up†	198	221	0·51 (−0·53 to 1·55)	0·34
Final score‡	220	252	0·15 (−0·89 to 1·19)	0·95

*Adjusted for differences in baseline score. A positive difference indicates a disadvantage for treatment arm 1 *v* arm 2.
†Based on last two ratings made in third and fourth years of follow up.
‡Based on last two ratings before interim analysis.

Table 5—*Number of patients with side effects and rate of side effects (per 1000 patient years) in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline)*

Side effects	Treatment arm 1		Treatment arm 2	
	No of patients	Rate	No of patients	Rate
Dyskinesia	79	93·2	98	106·1
Dystonia	70	78·7	88	93·1
Oscillations	108	139·7	120	132·4

patients in arm 2 was about 60% higher than that in arm 1, and there was no evidence that this treatment effect differed by sex or age.

To determine whether the excess mortality in arm 2 occurred while patients were still receiving their initial randomised treatment, the mortality data were also analysed with an "on treatment" approach, although this method is more subject to bias. Deaths were included only if they occurred while the patient was still receiving the initial treatment (70 out of the 120 deaths). For patients who had been withdrawn from the initial treatment, the years of follow up were calculated from date of entry to date of withdrawal from initial treatment. The ratio of mortality in arm 2 compared with arm 1 was 1·44 (0·89 to 2·33), similar to that obtained in the main "intention to treat" analysis.

Table 3 shows the causes of death in arms 1 and 2: Parkinson's disease was the commonest recorded cause of death. Postmortem confirmation of the diagnosis was available in only a small number of deaths.

DISABILITY

Analysis of Webster disability scores showed a similar pattern to that reported earlier,[9] and the difference in disability scores between arms 1 and 2 after four years of follow up was not significant, though arm 1 did have slightly worse scores than arm 2 (see table 4). Similar figures were seen with analysis of the North Western University disability scale. Figure 2 shows that, on average, patients in both arm 1 and arm 2 were returning towards their pretreatment level of disability by four years of follow up.

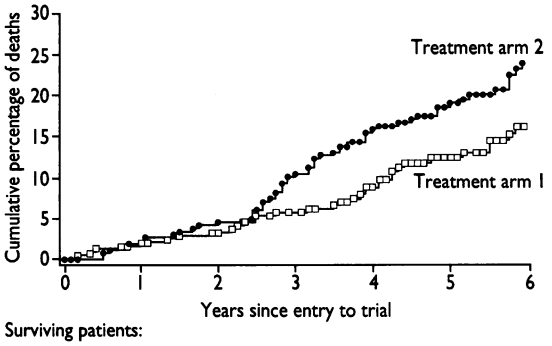
Table 5 shows the incidence of long term motor complications, with about 40% of patients in arm 1 and arm 2 having both motor fluctuations and dyskinesias. These two late complications usually, but not invariably, occurred together. The severity of interdose dyskinesias, however, was higher in arm 2; 40% of the dyskinesias were rated as moderate or severe, compared with only 25% in arm 1. Severe on/off effects were also slightly more common in arm 2; they comprised 33% of recorded oscillations, compared with 23% in arm 1.

Discussion

The absolute difference in mortality between arm 2 (levodopa with selegiline) and arm 1 (levodopa monotherapy) was 18.6 per 1000 patient years, which is equivalent to an extra death in the patients receiving levodopa and selegiline for every 54 patients treated for one year. We found no evidence that this effect differed with the age or sex of patients, and hazard ratios for males and females and younger and older patients were all similar. The Kaplan-Meier curves suggest that the difference in mortality started during the third year of follow up, but this should be interpreted with caution as the trial did not have enough power to detect early differences in mortality.

POSSIBLE BIAS

Mortality itself as an end point clearly cannot be biased, but the fact that the study was open raises the possibility that physicians' knowledge of patients' treatment could indirectly affect individual care,



Surviving patients:

Treatment arm 1	242	236	226	193	132	93
Treatment arm 2	263	256	240	209	153	108

Fig 1—*Cumulative percentage of deaths in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline): Kaplan-Meier estimate*

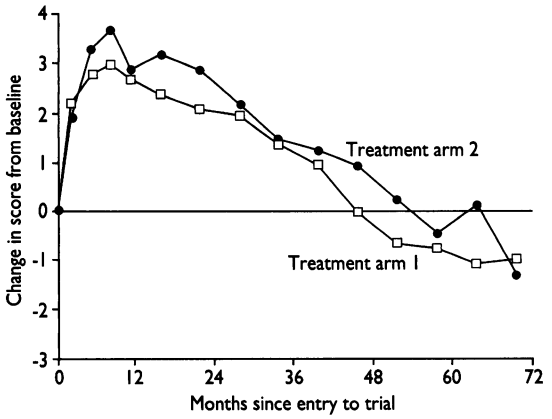


Fig 2—*Average change in Webster score of disability from baseline value in treatment arm 1 (levodopa alone) and arm 2 (levodopa and selegiline)*

possibly by influencing the decision on whether to withdraw a particular patient who was experiencing adverse events or showing a deteriorating response to treatment. If this was the case, however, one might expect that an "on treatment" analysis would produce different results, whereas it gave a similar hazard ratio. The number of patients withdrawn because of deteriorating response in the two arms did not differ greatly, and in fact more patients were withdrawn from treatment with levodopa and selegiline because of adverse reactions.

Furthermore, we had no a priori reason to believe that the patients receiving levodopa and selegiline would fare worse than those receiving levodopa monotherapy; the opposite would have been predicted from the previously reported studies.[4,12] The study by Birkmayer *et al*,[12] however, has several major deficiencies, including a retrospective, non-randomised design. Bias through non-blinding in our study also seems improbable as one would expect this, if anything, to be in favour of combined treatment with levodopa and selegiline. There was no difference in the severity of disease in the two groups before the start of treatment, and multivariate analyses showed that the hazard ratio was increased further after adjustment for other prognostic factors.

LEVODOPA SPARING EFFECT

Interestingly, the median daily dose of levodopa in arm 2 (levodopa and selegiline) did not increase over four years of sustained follow up. Investigators were at liberty to increase the dose of levodopa as much as they wished in order to achieve optimum motor control. The dose of levodopa required in arm 1 (levodopa alone) increased from a median of 375 mg a day after one year of treatment to 625 mg a day after four years. The unchanged dose in arm 2 indicates a levodopa sparing effect of 250 mg on average after four years of sustained treatment.

The similar deterioration in disability scores in the two study arms and the increased frequency of severe dyskinesias and motor oscillations in arm 2 make it unlikely that this finding is artefactual, related to a reluctance by the investigators to increase the dose of levodopa when it was used in combination with selegiline. It also provides further evidence for a significant symptomatic effect of selegiline when used as chronic treatment and raises the interesting possibility that the drug might become less selective to type B monoamine oxidase over time. Comparable levodopa sparing effects with selegiline have recently been reported in other randomised controlled trials.[18,19]

FURTHER STUDIES

The critical question is whether the relation between levodopa and selegiline and increased mortality is genuinely causal. Our trial subjects were patients with early, mild Parkinson's disease whose life expectancy over the follow up period was only slightly worse than that of the general population. (Compared with death rates for England and Wales, adjusted for each year, sex, and five year age band, the standardised mortality ratio for all three arms of the trial was 1·42 (95% confidence interval 1·23 to 1·65).) The precise cause of the increased mortality in arm 2 remains to be determined. Selegiline increased the number of early adverse events, and it is conceivable that it may have deleterious effects on the cardiovascular and cerebrovascular system. For example, in the DATATOP study a higher incidence of cardiac rhythm disturbance was reported in patients treated with selegiline.[5]

A detailed review of the hospital case notes and general practitioner records of the patients who died is proposed in which an independent review will be undertaken by a neurologist, a general practitioner, a geriatrician, and an epidemiologist. This panel will be blind to the classifications of cause of death based on the death certificates. In addition, we are carrying out tests of autonomic function and measurements of lying and standing blood pressure and pulse in those patients still participating in the trial. We are also exploring the possibility that adverse drug interactions between selegiline and serotonin reuptake inhibitors and other psychotropic drugs might be a relevant factor, even though serotonin is regarded as a substrate for type A monoamine oxidase. It seems unlikely that the somewhat higher dose of levodopa in arm 1 of the study might have reduced mortality because the two groups of patients had similar disability and currently available information does not indicate any important difference in mortality between patients with Parkinson's disease who are treated with maximum tolerated doses of levodopa and those given submaximum doses from the outset.[20]

Key messages

- It has been suggested that selegiline hydrochloride might have beneficial effects on the natural course of Parkinson's disease and improve life expectancy
- In an ongoing trial we have compared therapeutic effects of levodopa alone and levodopa combined with selegiline in patients with mild Parkinson's disease
- After average of 5·6 years' follow up, mortality was about 60% higher in patients given combined treatment than in those given levodopa alone, and this effect was independent of sex and age
- Disability scores were slightly, non-significantly higher in patients given levodopa alone, but severe motor complications were more frequent in patients given combined treatment
- Levodopa in combination with selegiline seemed to confer no clinical benefit over levodopa alone, and mortality was significantly higher with combination treatment

CONCLUSION

We conclude that combined treatment with levodopa and selegiline in patients with mild, previously untreated, Parkinson's disease seems to confer no detectable clinical benefit over treatment with levodopa alone. Furthermore, mortality was significantly increased in the patients given levodopa and selegiline. This is the first study to report such a finding. Analysis of mortality in other ongoing studies will be needed to see if this finding can be corroborated.

In the meantime the patients in arm 2 of our trial (levodopa and selegiline) will be informed of our results and advised to withdraw selegiline from their treatment regimens. These patients will then be reviewed after three months and their disabilities and requirements for levodopa reassessed. They will subsequently be assessed annually, and further mortality figures based on intention to treat will be obtained. We also propose to continue to follow patients in arm 1 (levodopa alone) and arm 3 (bromocriptine alone).

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Conflict of interest: None.

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Cancers coinciding with childbearing: delayed diagnosis during pregnancy?

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Cancers associated with childbearing pose extremely difficult questions for the patient and her physician. Population based registry data gave us the opportunity to examine the incidence of this uncommon occurrence.

Subjects, methods, and results

Cases were identified following a linkage between the Swedish Cancer Registry and a nationwide fertility registry. Nearly all diagnosed cancers are recorded in the cancer registry.[1] The fertility registry contains information on number and dates of live births for more than 2·3 million Swedish women born in 1925 and thereafter.[2]

Among women born from 1925 to 1972 more than 2·7 million live births and 32 848 cancers were recorded during reproductive ages (15-44 years) in 1960-90. Of all cancers, 428 (1·3%) were diagnosed during pregnancy (date of a live birth − 9 months) and 1425 (4·3%) during the lactation period (date of birth + 12 months). The overall incidences during pregnancy and lactation, respectively, were 15·6 and 51·6 per 100 000 live births.

Median age at diagnosis during pregnancy was 29·8 years. The most frequent sites were skin (malignant melanoma; 3·6 per 100 000 live births), cervix uteri (2·4 per 100 000), and breast (2·0 per 100 000). About 4% of breast cancers and 10% of thyroid cancers during reproductive years were diagnosed during pregnancy or in the year after birth. The corresponding figures in the age group 25-29, when childbearing was most frequent, were 19% and 21%, respectively.

Expected numbers during pregnancy and lactation were estimated from female age specific and period specific population rates. The observed to expected ratios during pregnancy were below unity for all of the 10 most common sites except melanoma. For all sites combined the observed to expected ratio was 0·4(9) [0·4(4)-0·5(3)]. For sites where case interval numbers indicated a deficit of recorded cases in early pregnancy (cervix uteri, breast, ovary, Hodgkin's disease, leukaemias), ratios were also computed based on observed numbers in trimester 3. During the lactation period the observed to expected ratio for all sites combined was 1·2(1) [1·1(5)-1·2(8)].

Comment

Our findings are in broad agreement with a previous population based study that observed fewer than expected cancers during pregnancy.[3] Our data indicate that a small, but not negligible, proportion of all malignancies in young women are diagnosed in association with childbearing. More importantly, the estimated observed to expected ratios suggest that diagnosis is delayed to the postpartum period. Pregnancy is usually a period of intense medical observation. However, potentially harmful diagnostic procedures are probably less likely to be implemented. Moreover, unusual signs and symptoms may be interpreted as being related to pregnancy. Given the physiological changes in the breast during childbearing this may be most evident for breast cancer; longer delays in pregnant compared with non-pregnant subjects have been reported.[4] In our data, fewer cases of breast cancer were diagnosed in the first half than in the second half of the lactation period.

An alternative explanation, but not mutually exclusive, is that tumour progression is altered during pregnancy and lactation. The growth of malignant cells, present before conception, may be stimulated by transient hormonal[5] and perhaps immunological changes during childbearing.

A limitation of our data was the lack of information on terminated pregnancies, which may have reduced the number of registered cases in the first and second